Role of Apixaban (Eliquis) in the Treatment And Prevention of Thromboembolic Disease

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INTRODUCTION

From the 1940s through 2010, warfarin (Coumadin, Bristol-Myers Squibb) was the only oral anticoagulant on the market in the U.S. for the treatment and prevention of thromboembolic disease. In 2010, the FDA approved dabigatran (Pradaxa, Boehringer Ingelheim), an oral direct thrombin inhibitor, for the prevention of thromboembolic events in patients with atrial fibrillation.[1] In 2011, rivaroxaban (Xarelto, Janssen), an oral factor Xa inhibitor, was the second novel oral anticoagulant to be approved in the U.S. for the prevention of deep vein thrombosis (DVT) after hip or knee replacement and for the prophylaxis of cerebrovascular accidents (CVAs) and systemic embolism in patients with nonvalvular atrial fibrillation.[2] Apixaban (Eliquis, Bristol-Myers Squibb) is the third novel oral anticoagulant to be approved in the U.S. for the management of thromboembolic disease.

Apixaban is a potent, direct, selective factor Xa inhibitor that was approved on December 28, 2012. This article reviews the pharmacology, pharmacodynamics, pharmacokinetics, clinical efficacy, and safety data for this agent.

PHARMACOLOGY

Apixaban, a pyrazole derivative, is chemically described as 1-(4-methoxy-

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phenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl) phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4c] pyridine-3-carboxamide.[3] Its molecular formula is $C_{25}H_{25}N_5O_4$, and its molecular weight is 459.[4,5] The chemical structure of apixaban is depicted in Figure 1.

Apixaban produces its antithrombotic effect by directly and selectively inhibiting free and clot-bound factor Xa.[3,5] Inhibition of factor Xa leads to decreased conversion of factor II (prothrombin) to IIa, resulting in decreased thrombin generation.

Apixaban is 30,000-fold more selective for factor Xa than other biological human coagulation proteases and does not require the presence of antithrombin III to inhibit factor Xa.[4] Apixaban does not directly affect activated protein C, factors IXa and VIIa, or thrombin.[3] In addition, apixaban is an indirect inhibitor of platelet aggregation, suggesting that it might be useful in the management of venous and arterial thromboembolism.[4]

Pharmacodynamics

The onset of anticoagulation following a single dose of apixaban is 1 to 3 hours.[6] Apixaban administration results in a dose-dependent increase in activated partial thromboplastin time (aPTT), the International Normalized Ratio (INR), modified prothrombin time (PT), and anti–factor Xa activity.[7] The effect of apixaban on the INR is highly variable and dependent on drug concentrations. The modified PT and anti–factor Xa levels are more sensitive than the prothrombin time (PT) to the effects of apixaban.[6] In addition, based on one phase 2 study in Japanese patients (ARISTOTLE-J; see page 209), anti-Xa activity correlated closely with apixaban concentrations, whereas the correlation with PT, INR, and aPTT was weak.[8]

Apixaban does not increase bleeding time.[4,6,7] According to the available literature, it appears that the most appropriate laboratory-

monitoring test for apixaban is the anti–factor Xa level. However, a target anti–factor Xa level has not been established for apixaban, and routine laboratory monitoring is not currently recommended.[6] The pharmacodynamic properties of apixaban are summarized in Table 1.

Pharmacokinetics

Apixaban follows linear pharmacokinetics.[7] Following oral administration, peak plasma levels (C_{max}) of the drug are reached in 1 to 3 hours.[7,9] Apixaban is absorbed in the stomach and in the small intestine, and the absolute bioavailability is equal to 50%.[5,10] Plasma protein binding in humans is approximately 87%.[10] The volume of distribution is 21 L,[5] suggesting limited distribution to the extravascular tissue.

Apixaban is eliminated via multiple pathways in humans (i.e., O-demethylation, hydroxylation, and O-demethylation followed by sulfation).[11] The drug is metabolized primarily by cytochrome P450 (CYP) 3A4/5. Isoenzymes CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19 provide minor contributions to the metabolism of apixaban.[5,11] The metabolism of apixaban results in the formation of inactive metabolites, including O-demethyl apixaban sulfate (M_1), O-demethyl apixaban (M_2), 3-hydroxy apixaban (M_7), and hydroxylated O-demethyl apixaban (M_{13}).[4–6,9,12] Apixaban is also a substrate
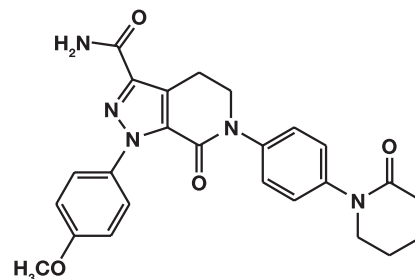

Figure 1 Chemical structure of apixaban (Eliquis). (Data from prescribing information.[5])

for P-glycoprotein (P-gp) and the breast cancer resistance protein transporter.[4,6] Apixaban does not significantly inhibit or induce isoenzymes CYP 3A4, 1A2, 2C8, 2C9, 2C19, 2D6, or 3A4.[11]

Apixaban is eliminated via renal and fecal routes. Approximately 25% of apixaban is excreted in the urine, primarily as unchanged drug. Another 56% of apixaban is eliminated in the feces, with more than 50% as the parent compound.[9,13] The elimination half-life has been reported to be 8 to 15 hours.[9,10]

A single 10-mg dose, when administered to healthy patients, resulted in an increased C_{max} and area-under-the-curve (AUC) concentration in patients weighing less than 50 kg and a decreased C_{max} and AUC concentration in patients weighing more than 120 kg.[3] An increased C_{max} and AUC concentration were also observed when apixaban 10 mg was given to patients older than 65 years of age (compared with healthy younger adults) and to women.[3] The C_{max} of apixaban does not appear to be affected by the presence of renal insufficiency. However, the AUC concentration was increased by 16% in patients with a creatinine clearance (CrCl) of 51 to 80 mL/minute, by 29% in patients with a CrCl of 30 to 50 mL/minute, and by 44% in patients with a CrCl of 15 to 30 mL/minute.[6] The pharmacokinetic properties of apixaban do not appear to be affected by Asian ethnicity, African-American ethnicity, or food.[3,7]

The pharmacokinetic properties of apixaban are summarized in Table 2.

Table 1 Pharmacodynamic Properties of Apixaban (Eliquis)

Variable*	Value
Maximum aPTT increase from baseline	1.2 times baseline
Maximum INR prolongation from baseline	1.5 times baseline
Maximum modified PT % prolongation from baseline	3 times baseline
Mean time to maximum effect	2.5–3.3 hours

*Based on single dose ranging from 0.5 mg to 50 mg.
aPTT = activated partial thromboplastin time; INR = International Normalized Ratio; PT = prothrombin time.

CLINICAL TRIALS
Acute Coronary Syndrome
The APPRAISE Trial[14]

APPRAISE was an international, multicenter, randomized, double-blind, placebo-controlled phase 2 dose-escalation study that was conducted to evaluate the safety and efficacy of apixaban in preventing recurrent ischemic events after acute coronary syndrome (ACS). Patients (n = 1,715) with recent ST-elevation or non–ST-elevation myocardial infarction (MI) were randomly assigned to one of five treatment groups: placebo, apixaban 2.5 mg orally twice daily, apixaban 10 mg once daily, apixaban 10 mg twice daily, or apixaban 20 mg once daily. Treatment was continued for 6 months. Most patients were Caucasian men (average age, 60 years). Almost all patients were receiving aspirin, and more than 75% of patients also received clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi). The average time to the start of study drug was 4 days.

The primary efficacy outcome was the composite of cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke. The primary safety endpoint was the incidence of major or clinically relevant non-major bleeding.

There were no statistically significant differences in the primary efficacy outcome among the treatment groups: 8.7% for placebo, 7.6% for apixaban 2.5 mg twice daily ($P = 0.21$ vs. placebo), and 6.0% for apixaban 10 mg once daily ($P = 0.07$ vs. placebo). Rates of adverse events were lower in patients who were not taking clopidogrel.

The incidence of major and clinically relevant non-major bleeding was 3.0% in the placebo group, 5.7% in the apixaban 2.5-mg twice-daily group ($P = 0.09$ vs. placebo), and 7.9% in the apixaban 10-mg once-daily group ($P = 0.005$ vs. placebo). The most commonly reported types of bleeding were bruising, epistaxis, hematoma, hematuria; gastrointestinal (GI) and gingival sites were also affected. Except for GI tract bleeding, rates of bleeding were higher in patients receiving apixaban 10 mg daily. Patients receiving clopidogrel were more likely to experience bleeding. There was no difference in the incidence of elevated hepatic transaminases (ALT or AST) among patients receiving apixaban.

The authors concluded that the use of apixaban, in addition to current standard antiplatelet therapy in patients with recent ACS, was associated with a dose-dependent increase in bleeding and a trend toward a lower number of ischemic events.

The APPRAISE-2 Trial[15]

Alexander et al. conducted a double-blind, placebo-controlled, randomized phase 3 clinical trial to evaluate whether the reduction in ischemic events, pre-

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Clinical Trials

ADOPT: Apixaban Dosing to Optimize Protection from Thrombosis
ADVANCE-1: Apixaban Dose Orally vs. Anticoagulation with Enoxaparin 1
ADVANCE-2: Apixaban Dose Orally vs. Anticoagulation with Enoxaparin 2
ADVANCE-3: Apixaban Dosed Orally vs. Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism 3
AMPLIFY–EXT: Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy-Extended Treatment
APPRAISE: Apixaban for Prevention of Acute Ischemic and Safety Events
APROPOS: Apixaban Prophylaxis in Patients Undergoing Total Knee Replacement Surgery
ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ARISTOTLE-J: Safety and Efficacy of Apixaban in Japanese Patients with Nonvalvular Atrial Fibrillation
AVERROES: Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment

Table 2 Pharmacokinetic Properties of Apixaban (Eliquis)	
Variable	**Value**
Administration	Oral
Peak plasma concentration	1–3 hours
Bioavailability	~50%
Volume of distribution	21 liters
Protein binding	87%
Metabolism	Hepatic via cytochrome P450 3A4/5
Elimination	Renal: 25% Biliary: 56%
Half-life	8–15 hours

viously noted with the use of apixaban, would outweigh the increase in incidence of bleeding events in a high-risk population with ACS.

Patients (n = 7,392) with at least two risk factors (such as age older than 65 years, diabetes mellitus, a history of a previous MI, cerebrovascular disease, peripheral vascular disease, a history of heart failure, or impaired renal function) were assigned to receive either apixaban 5 mg twice daily or matching placebo. The median duration of treatment was 240 days. Almost all patients (97%) were receiving aspirin, and about 81% of patients were receiving dual antiplatelet therapy with aspirin and clopidogrel or another P_2Y_{12}-receptor antagonist.

The primary efficacy outcome was the composite of cardiovascular death, MI, or ischemic stroke. The primary safety endpoint was major bleeding. Prespecified secondary outcomes included the primary efficacy outcome plus unstable angina, hemorrhagic stroke, or fatal bleeding and the composite of death from any cause, MI, or ischemic or hemorrhagic stroke. The primary safety outcome was major bleeding.

The primary efficacy outcome occurred in 7.5% of patients receiving apixaban and in 7.9% of patients receiving placebo (P = 0.51). There were no statistically significant differences between apixaban and placebo groups in any of the individual components of the primary or secondary efficacy outcome. There were also no statistically significant differences in efficacy between patients receiving aspirin and apixaban in combination compared with those receiving triple antithrombotic therapy with aspirin, apixaban, and a P_2Y_{12}-receptor antagonist.

Adverse events, as well as serious adverse events, occurred in 59% and 24.3% of patients, respectively, in the apixaban group and 57.7% and 24.3% of patients, respectively, in the placebo group. Major bleeding was reported in 0.5% of placebo patients and in 1.3% of apixaban patients (P = 0.001). There was no significant difference in the frequency of liver enzyme elevations to greater than three times the upper limit of normal (ULN) (0.7% for apixaban and 0.8% for placebo; P = 0.573).

The study was discontinued prematurely because of a high rate of major bleeding events and the absence of a statistically significant difference in efficacy.

The authors concluded that the addition of apixaban to standard antiplatelet therapy in high-risk patients following an ACS did not result in a significant reduction in ischemic events; however, the drug significantly increased the number of major bleeding events.

Atrial Fibrillation
The AVERROES Trial[16,17]
Connolly et al. conducted a randomized, multicenter, double-blind, double-dummy phase 3 clinical trial to evaluate whether apixaban was superior to aspirin in preventing thromboembolic events in patients with atrial fibrillation who were not candidates for vitamin K antagonist therapy.

A total of 5,599 eligible patients (average age, 70 years) and a mean $CHADS_2$ (Congestive Heart Failure, Hypertension, Age > 75, Diabetes, and Stroke) score equal to 2 received apixaban 5 mg orally twice daily or aspirin. A reduced dose of apixaban (2.5 mg twice daily) was administered to patients who met at least two of the following criteria: age older than 80 years, body weight of 60 kg or less, and serum creatinine level of 1.5 mg/dL or higher. The aspirin dose ranged from 81 mg to 324 mg daily and was determined by the treating physician. Most of the patients had a history of hypertension (86%) and 14% of patients had a history of stroke or of transient ischemic attack.

The primary efficacy endpoint was the occurrence of ischemic or hemorrhagic stroke or systemic embolism. The primary safety outcome was the occurrence of major bleeding. Additional outcomes were the rate of MI, death from vascular causes, death from any cause, and composites of major vascular events.

The primary efficacy outcome was observed at rates of 1.6% per year in the apixaban group and 3.7% per year in the aspirin group (P < 0.001). The rates of ischemic stroke were 1.1% and 3% per year for apixaban and aspirin, respectively (P < 0.001). Systemic embolism occurred in 0.1% of patients receiving apixaban and in 0.4% of patients receiving aspirin (P = 0.01). Hospitalization rates differed significantly, affecting 12.6% of those receiving apixaban and 15.9% of those receiving aspirin (P < 0.001).

Rates of hemorrhagic stroke did not differ significantly for apixaban and aspirin (0.2% vs. 0.3%, respectively; P = 0.45). In a subgroup analysis by Diener et al., apixaban was similarly effective in preventing thromboembolic events in patients with atrial fibrillation whether or not these patients had had a previous stroke or a transient ischemic attack.[17]

There was a significant difference in the rate of serious adverse events in the apixaban group (22%) compared with the aspirin group (27%) (P < 0.001). There was no difference in rates of major bleeding between the two treatment groups: 1.4% per year with apixaban and 1.2% per year with aspirin (P = 0.57).

The authors concluded that apixaban was superior to aspirin in reducing the risk of stroke or systemic embolism in patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable without a significant increase in the risk of major bleeding.

The ARISTOTLE Trial[18,19]

ARISTOTLE was a randomized, double-blind, double-dummy phase 3 clinical trial that was conducted to compare the effects of apixaban to warfarin in reducing the risk of stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.

A total of 18,201 patients (average age, 70 years) with a mean CHADS₂ score of 2.1 received either apixaban 5 mg orally twice daily or dose-adjusted warfarin (a target INR of 2.0 to 3.0). The apixaban dose was reduced to 2.5 mg twice daily if the patient met at least two of the following criteria: age at least 80 years, weight no more than 60 kg, or a serum creatinine level of 1.5 mg/dL or higher. The mean duration of treatment was 1.8 years.

The primary efficacy endpoint was to determine whether apixaban was noninferior to warfarin for preventing stroke or systemic embolism in patients with atrial fibrillation and an additional risk factor for stroke. The primary safety endpoint was major bleeding. The secondary efficacy endpoint was to determine whether apixaban was superior to warfarin with respect to primary efficacy and safety endpoints.

The incidence of stroke or systemic embolism was 1.27% per year in apixaban patients and 1.6% per year in warfarin patients ($P < 0.001$ for non-inferiority; $P < 0.01$ for superiority). Incidence rates of hemorrhagic stroke were 0.24% for the apixaban patients and 0.47% per year for the warfarin group ($P < 0.001$). There was no statistically significant difference in the rate of ischemic stroke and systemic embolism between the warfarin and apixaban groups. Death from any cause was reported at rates of 3.52% per year in apixaban patients and 3.94% per year in warfarin patients ($P = 0.047$). The effects of apixaban versus warfarin were consistent in patients with atrial fibrillation with and without previous stroke or transient ischemic attack.[19]

Overall, there was no significant difference in the frequency of serious adverse events between the groups (35% with apixaban and 36.5% with warfarin). Rates of major bleeding were 2.13% per year in apixaban patients and 3.09% per year in warfarin patients ($P < 0.001$). Intracranial hemorrhage occurred at the rate of 0.33% in apixaban patients and 0.80%

in warfarin patients ($P < 0.001$). Rates of GI bleeding were similar (apixaban, 1.79%, and warfarin, 2.27%; $P = 0.37$). The study drug was discontinued secondary to an adverse event in 7.6% of patients receiving apixaban and in 8.4% of patients receiving warfarin.

The authors concluded that apixaban was superior to warfarin in reducing the risk of stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke. The drug was also judged to be associated with a lower risk of bleeding compared with warfarin.

The ARISTOTLE-J Trial[8]

Ogawa et al. conducted a randomized, partially blinded, active-controlled phase 2 clinical study that aimed to evaluate the risk of major and clinically relevant non-major bleeding of two doses of apixaban and open-label warfarin in the Japanese population with nonvalvular atrial fibrillation and one additional risk factor for stroke.

A total of 222 patients (mean age, 70 years) were assigned to one of three groups: apixaban 2.5 mg orally twice daily, apixaban 5 mg twice daily, or warfarin. In patients younger than age 70, the warfarin dose was titrated to an INR of 2.0 to 3.0, and in patients older than age 70, the warfarin dose was titrated to an INR of 2.0 to 2.6. The duration of treatment was 12 weeks. More than 80% of the patients were men. Average CHADS₂ scores were 1.8 in the apixaban 2.5-mg twice-daily group, 2.1 in the apixaban 5-mg twice-daily group, and 1.9 in the warfarin group.

The primary safety outcome was a composite of major bleeding and clinically relevant non-major bleeding events. Efficacy outcomes included a composite of stroke or systemic embolism; a composite of stroke, systemic embolism, or all-cause death; and a composite of MI or all-cause death.

Major bleeding or clinically relevant non-major bleeding occurred in 1.4% of patients receiving apixaban 2.5 mg twice daily, in 1.4% of patients receiving apixaban 5 mg twice daily, and in 5.3% of patients receiving warfarin. Minor bleeding was reported in 23.9% of patients receiving apixaban 5 mg twice daily, in 12.5% of patients receiving apixaban 2.5 mg twice daily, and in 17.3% of patients receiving warfarin. The most common

types of minor bleeding were epistaxis and hematuria.

As for efficacy outcomes, no strokes, systemic emboli, MI, or deaths were reported in either apixaban group of patients. In the warfarin group, stroke was reported in 4.1% of patients. Nasopharyngitis was the most commonly reported non-bleeding adverse event, occurring at rates of 11.3% for apixaban 5 mg twice daily, 11.1% for apixaban 2.5 mg twice daily, and 9.3% for warfarin.

The authors concluded that both apixaban doses were well tolerated by Japanese patients with documented nonvalvular atrial fibrillation and at least one additional risk factor for stroke. Rates of major or clinically relevant non-major bleeding events were lower with both apixaban treatments compared with warfarin.

Venous Thromboembolism: Prevention

The APROPOS Trial[20]

A randomized, eight-arm, parallel-group, multicenter phase 2 trial was conducted by Lassen et al. to evaluate the efficacy and safety of six dosing regimens of apixaban compared with enoxaparin (Lovenox, Sanofi) or warfarin for preventing venous thromboembolism (VTE) following total knee replacement.

Patients (n = 1,238) were assigned to one of eight treatment groups: warfarin titrated to a target INR of 1.8 to 3, subcutaneous (SQ) enoxaparin 30 mg every 12 hours, apixaban 5 mg daily, apixaban 10 mg daily, apixaban 20 mg daily, apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, or apixaban 10 mg twice daily. Treatment was initiated 12 to 24 hours after surgery and continued for an average of 12 days. Most patients (mean age, 66.7 years) were Caucasian (93%), and 63.3% were women. The primary efficacy endpoint was a composite of VTE events or death from any cause. The primary safety endpoint was major bleeding.

The rate of asymptomatic DVT was lower for patients receiving apixaban (5%–11%) compared with 14% of patients in the enoxaparin group and 28% in the warfarin group. A similar trend was seen in total VTE among apixaban, enoxaparin, and warfarin groups. Among the apixaban groups, the rate of total VTE was lower with apixaban 5 mg twice daily and 10 mg twice daily (5% and 6%, respective-

ly) compared with the apixaban once-daily regimens (9%–13%). Three patients died during the study period, all in the apixaban treatment groups.

The incidence of major bleeding ranged from 0% to 5% for patients receiving apixaban compared with 0% for those receiving enoxaparin and warfarin. Minor bleeding occurred in 1% to 11% of apixaban patients, in 6% of enoxaparin patients, and in 8% of warfarin patients. A dose response was noted for the incidence of minor bleeding within the daily and twice-daily apixaban groups.

The authors concluded that apixaban at doses of 2.5 mg twice daily or 5 mg daily might be effective in preventing VTE after total knee replacement.

The ADOPT Trial[21]

An international, multicenter, randomized, double-blind, controlled study, ADOPT was conducted to evaluate the efficacy and safety of apixaban in extended prophylaxis of VTE in acutely ill medical patients. A total of 6,528 patients (mean age, 67 years) with moderate or severe restrictions in mobility received apixaban 2.5 mg twice daily for 30 days (n = 3,255) or SQ enoxaparin 40 mg daily for a minimum of 6 days (n = 3,273). Most patients were Caucasian; 47% of patients had a history of heart failure, and 52% of patients had a history of chronic obstructive pulmonary disease (COPD). On average, patients received apixaban for 24.9 days and enoxaparin for 7.9 days.

The primary efficacy endpoint was a composite of death related to VTE, fatal or nonfatal pulmonary embolism, symptomatic DVT, or asymptomatic proximal-leg DVT. Primary safety endpoints were major bleeding, clinically relevant non-major bleeding, and all bleeding reported by investigators.

Incidence rates for the primary efficacy endpoint were 2.71% for apixaban and 3.06% for enoxaparin ($P = 0.44$). There were no significant differences in the individual outcomes of the composite endpoint between the two treatment groups. Bleeding occurred in 7.73% of apixaban patients and in 6.81% of enoxaparin patients ($P = 0.18$). The difference in rates of major bleeding between the two treatment groups was statistically significant: 0.47% in patients receiving apixaban and 0.19% in patients receiving enoxaparin ($P = 0.04$). There were no significant dif-

ferences in rates of death, MI, stroke, thrombocytopenia, or elevation of liver enzymes among the two treatment groups.

In this trial, apixaban failed to demonstrate superiority to a short-term course of enoxaparin in medically ill patients for preventing VTE. Rates of major bleeding were significantly higher with apixaban compared with enoxaparin.

The ADVANCE-1 Trial[22]

Lassen et al. conducted a randomized, double-blind, double-dummy phase 3 clinical study that evaluated whether apixaban was non-inferior to enoxaparin in preventing VTE after knee replacement. Patients (mean age, 66 years) who were scheduled for total knee replacement surgery or revision of a previously inserted transplant (n = 3,195) were randomly assigned to receive apixaban 2.5 mg orally twice daily (n = 1,599) or SQ enoxaparin 30 mg every 12 hours (n = 1,588). The mean time to administration of the study drug was 20.3 hours in the apixaban group and 20.2 hours in the enoxaparin group. Patients received apixaban for an average of 11.7 days and enoxaparin for 11.6 days.

The primary efficacy endpoint was the composite of asymptomatic and symptomatic DVT, nonfatal pulmonary embolism, or death from any cause during the treatment. The primary safety endpoint was the composite of major and clinically relevant non-major bleeding during the treatment period or until 2 days after the last dose administration.

There were no significant differences in the primary efficacy endpoint: 9.0% of patients in the apixaban group and 8.8% of patients in the enoxaparin group were affected ($P = 0.06$). There were also no significant differences in the individual components of the primary composite endpoint between the two treatment groups.

As for the frequency of drug-related adverse events, there were no significant differences between treatment groups (20.5% for apixaban vs. 21.7% for enoxaparin). Bleeding occurred in 6.9% of patients receiving apixaban and in 9.1% of patients receiving enoxaparin. Major or clinically relevant non-major bleeding was reported in 2.9% of apixaban patients and in 4.3% of enoxaparin patients ($P = 0.03$).

The incidence of major bleeding did not differ significantly between groups:

0.7% of the apixaban patients and 1.4% of the enoxaparin patients were affected ($P = 0.053$). A total of 8.5% of patients in the apixaban group and 8.6% of patients in the enoxaparin group experienced at least one serious adverse event during the study period. Rates of hepatic enzyme elevations were 1.1% for apixaban and 1.7% for enoxaparin. Additional adverse events occurring in more than 5% of the patients included constipation, nausea, pyrexia, edema, dizziness, vomiting, pain in the extremities, and insomnia. There was no significant difference in the frequency of these adverse effects between the two treatment groups.

Although the rates of the primary efficacy endpoint between the apixaban group and the enoxaparin group appeared to be similar, the trial did not meet statistical criteria to show non-inferiority in this endpoint. However, apixaban was associated with significantly lower rates of bleeding events compared with SQ enoxaparin 30 mg twice daily.

The ADVANCE-2 Trial[23]

ADVANCE-2 was a multicenter, randomized, double-blind, non-inferiority phase 3 study that evaluated the efficacy of oral apixaban 2.5 mg twice daily compared with oral enoxaparin 40 mg every 24 hours for the prevention of VTE following total knee replacement. A total of 3,057 patients (mean age, 67 years) were enrolled. Patients received the first dose of enoxaparin within 12 hours before surgery. The first dose of apixaban was administered 12 to 24 hours after the procedure.

The primary efficacy endpoint was the composite of asymptomatic DVT, nonfatal pulmonary embolism, and all-cause mortality. The primary safety endpoint measure was bleeding.

There was a statistically significant difference in rates of primary efficacy outcomes: 15.06% vs. 24.37% ($P < 0.0001$) for apixaban versus placebo. There was also a statistically significant difference in rates of major VTE between the two treatment groups (1.09 for apixaban and 2.17% for enoxaparin; $P = 0.0186$). There was no difference in rates of symptomatic DVT or in rates of death related to VTE among the two treatment groups.

Fifty-two percent of patients in the apixaban group and 55% of patients in the enoxaparin group experienced an

adverse drug event. Nausea, vomiting, and constipation occurred in more than 5% of patients. An adverse event was considered to be drug-related in 14% of patients in each of the treatment groups. An adverse event resulting in drug discontinuation was reported in 3% of patients in each treatment group.

Bleeding was reported in 6% of patients receiving apixaban and in 7% of patients receiving placebo. There were no significant differences in rates of major bleeding between the two groups (0.6% for apixaban vs. 0.9% for enoxaparin; $P = 0.3014$) or in rates of hepatic enzyme elevations to more than three times the ULN (2% for each group), thrombocytopenia, MI, or stroke.

In this trial, apixaban 2.5 mg twice daily was more effective than SQ enoxaparin 40 mg daily, without an increase in bleeding risk, in preventing VTE after total knee replacement.

The ADVANCE-3 Trial[24]

ADVANCE-3, an international, randomized, double-blind, double-dummy phase 3 clinical trial, was conducted to compare the efficacy and safety of apixaban and enoxaparin in preventing VTE in patients undergoing elective hip replacement.

A total of 5,407 patients (mean age, 60 years) received either apixaban 2.5 mg orally twice daily, starting 12 to 24 hours after closure of the surgical wound, or SQ enoxaparin 40 mg once daily, starting 12 hours before surgery. Patients received the study drug for a mean of 34 days. Of note, 59.5% of patients received a concomitant nonsteroidal anti-inflammatory drug (NSAID).

The primary efficacy endpoint was the composite of asymptomatic or symptomatic DVT, nonfatal pulmonary embolism, or death from any cause during the treatment period. The primary safety outcome was the composite of major and clinically relevant non-major bleeding during the treatment period or until 2 days after the last dose was administered.

Incidence rates for the primary efficacy endpoint were 1.4% with apixaban and 3.9% with enoxaparin ($P < 0.001$). Rates of major VTE were significantly lower in patients treated with apixaban than in those receiving enoxaparin (0.5% vs. 1.1%, respectively; $P = 0.01$). There were no statistically significant differences in rates of symptomatic DVT and death from

VTE between the groups (0.1% vs. 0.4%, respectively, for apixaban vs. placebo; $P = 0.11$).

Bleeding was reported in 11.7% of patients in the apixaban group and in 12.6% of patients in the enoxaparin group ($P = 0.34$). There were no differences in major bleeding rates between the two treatment groups: 0.8% for apixaban and 0.7% for enoxaparin ($P = 0.54$) or in the percentage of patients experiencing elevated hepatic enzymes greater than three times the ULN (1.4% vs. 1.8%, respectively). The rates of MI, stroke, and thrombocytopenia were similar for the two treatment groups.

Similar to the findings in ADVANCE-2, apixaban 2.5 mg twice daily was considered superior to enoxaparin 40 mg daily for the prophylaxis of VTE inpatients undergoing hip replacement surgery. Both of these treatment regimens resulted in similar rates of bleeding.

Venous Thromboembolism: Treatment

The AMPLIFY–EXT Trial[25]

Agnelli et al. conducted a randomized, double-blind study to evaluate the efficacy and safety of apixaban in extended treatment of VTE. Patients (n = 2,486) (mean age, 57 years) received apixaban 2.5 mg twice daily (n = 842), apixaban 5 mg twice daily (n = 815), or placebo (n = 829). All patients had an objectively confirmed symptomatic DVT or pulmonary embolism and had been treated with standard thromboembolic therapy for 6 to 12 months. The thromboembolic event was unprovoked in more than 90% of patients. The use of aspirin at doses exceeding 165 mg daily, dual antiplatelet therapy, and potent inhibitors of CYP3A4 and P-gp was prohibited.

The primary efficacy endpoint was the composite of symptomatic recurrent VTE or death from any cause. The primary safety outcome was major bleeding.

There was a statistically significant difference in rates of the primary composite endpoint between the groups: 3.8% for apixaban 2.5 mg, 4.2% for apixaban 5 mg, and 11.6% for placebo ($P < 0.001$ for apixaban vs. placebo). The difference in the rate of the primary composite outcome between the two apixaban groups was not statistically significant.

The same trend was seen for rates of recurrent VTE or VTE-related death: 1.7%

of patients receiving apixaban 2.5 mg, 1.7% of patients receiving apixaban 5 mg, and 8% receiving placebo ($P < 0.001$ for both apixaban groups vs. placebo).

Eight percent of patients who were assigned to apixaban 2.5 mg twice daily, 7.5% of patients assigned to apixaban 5 mg twice daily, and 16.2% of patients assigned to placebo experienced an adverse event that led to discontinuation of therapy. Major bleeding occurred in 0.2% of patients receiving apixaban 2.5 mg, in 0.1% of patients receiving apixaban 5 mg, and in 0.5% of patients receiving placebo. Clinically non-major bleeding occurred in 3.2% of patients receiving apixaban 2.5 mg, in 4.3% of patients receiving apixaban 5 mg, and in 2.3% of patients receiving placebo. This difference was statistically significant for apixaban 5 mg compared with placebo.

The trial findings suggested that apixaban 2.5 mg twice daily and apixaban 5 mg twice daily, given for an additional 12 months following a standard anticoagulant therapy, were superior to placebo in reducing recurrent VTE without an increased risk of major bleeding events.

DRUG INTERACTIONS

According to the product information for apixaban, coadministration with aspirin or clopidogrel did not affect the pharmacodynamics of apixaban.[5] However, the risk of bleeding events was higher when apixaban was given with aspirin and clopidogrel in the APPRAISE-2 trial.[15] Coadministration of apixaban with NSAIDs or enoxaparin resulted in a 50% to 60% increase in anti-FXa activity.[3,5] Coadministration of apixaban with digoxin had no effect on the pharmacokinetics of digoxin (Lanoxin, GlaxoSmithKline).[10]

Apixaban is a substrate for CYP3A4 and P-gp; therefore, the concomitant administration of apixaban with drugs that inhibit or induce CYP3A4 or P-gp may affect the disposition of apixaban.[5] Administering apixaban with ketoconazole (Nizoral, Pfizer), a strong inhibitor of CYP3A4 and P-gp, resulted in a significant increase in apixaban concentrations.[3,4]

Diltiazem (Cardizem, Biovail/Valeant) coadministration resulted in a moderate increase in apixaban exposure.[3] Coadministration of naproxen (Naprosyn, Roche), a P-gp inhibitor, resulted in a 1.5-fold to 1.6-fold increase in mean apixaban C_{max} and AUC concentration.[3] A 50% decrease

in apixaban exposure was observed after coadministration with rifampin (Rifadin, Sanofi).[4]

The concomitant use of apixaban with other strong inducers of CYP3A4 and P-gp, such as phenytoin (Dilantin, Pfizer), carbamazepine (Carbatrol, Shire), phenobarbital, or St. John's wort, may lead to reduced plasma apixaban levels.[3,4] The manufacturer recommends against the use of apixaban in patients who are taking strong inducers of CYP3A4.[5] Apixaban has not been shown to induce or inhibit CYP3A4 or P-gp.[5,6,11]

SAFETY AND TOLERABILITY

The most commonly reported adverse effect in clinical trials of apixaban was bleeding. The rate of major bleeding with a dose of 5 mg twice daily was reported as 2.13% or less.[8,16,18,19,25] The most common site of major bleeding was the GI tract. In the trials, intracranial hemorrhage occurred at a rate of less than 1%.[8,16,18,19,25] Minor bleeding events included bruising, epistaxis, hematoma, and hematuria. Gingival sites were also affected. Rates of bleeding with apixaban were lower than those reported with warfarin.

Adverse effects unrelated to bleeding in clinical trials included nasopharyngitis, nausea, vomiting, and constipation.[23] Allergic reactions occurred in fewer than 1% of patients receiving apixaban.[5] Elevations in liver enzymes were rare and occurred at the same incidence as with the comparator drugs.[8,16,18–21,23–25]

DOSAGE AND ADMINISTRATION

The recommended dose of apixaban is 5 mg twice daily when used to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[5] The dose should be reduced to 2.5 mg twice daily in patients receiving concomitant drugs that are dual inhibitors of CYP3A4 and P-gp and in patients with two of the following factors: age older than 80 years, body weight below 60 kg, or serum creatinine above 1.5 mg/dL.[5] Apixaban should not be used in patients with severe hepatic dysfunction and in those with a CrCl of below 15 mL/minute.[5]

COST

The average wholesale price (AWP) of apixaban is $5 per tablet, regardless of tablet strength.[26] Therefore, if apixaban is given at the recommended dose, the AWP for a patient for 30 days would be approximately $300. The AWP of rivaroxaban is $10 per tablet;[27] the AWP of dabigatran is approximately $5 per tablet.[28] Hence, the cost of apixaban is comparable to that of the other novel oral anticoagulants.

The AWP of warfarin is $0.58 to $0.99 per tablet. Because warfarin is taken once daily, the AWP for a patient for 30 days is approximately $17.40 to $29.70.[29] Although the AWP of warfarin is significantly lower than apixaban, a pharmacoeconomic analysis demonstrated that apixaban might be more cost-effective because of the decreased need for laboratory monitoring and the lower rates of stroke or systemic embolism.[30]

P&T COMMITTEE CONSIDERATIONS

Apixaban is an oral selective factor Xa inhibitor. Clinical trial data suggest that apixaban is more effective than warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke, without increasing the risk of bleeding. Apixaban has also been an effective alternative to enoxaparin in preventing thromboembolic events following hip and knee replacement. Apixaban does not seem to have a role in the management of ACS. The role of apixaban in preventing thromboembolic events in medically ill patients and in treating acute VTE has not been well established.

We did not find any trials directly comparing apixaban with other novel anticoagulants. Indirect comparisons of the three novel agents suggest that rivaroxaban, dabigatran, and apixaban do not differ significantly in terms of efficacy and safety.[31]

Based on the drug's safety and efficacy data, and based on the fact that its price is similar to that of rivaroxaban and dabigatran (although costlier than warfarin), we recommend that apixaban be added to formulary. However, we recommend restricting apixaban to patients who are not candidates for warfarin because of labile INRs, drug–drug interactions, or noncompliance with laboratory monitoring. Apixaban may be considered an alternative agent to dabigatran and rivaroxaban.

CONCLUSION

Apixaban is a direct, selective factor Xa inhibitor that is well tolerated when taken orally twice daily for the prevention of stroke in patients with atrial fibrillation and for the prevention of VTE following knee or hip replacement. The drug was found to be superior to warfarin in clinical trials in preventing thromboembolic events in patients with atrial fibrillation and an additional risk of stroke. The most common adverse event of apixaban is bleeding. Although the frequency of bleeding appears to be similar to that for warfarin, the potential risk of major bleeding is lower with apixaban.

The potential for drug interactions with apixaban is lower than that with warfarin. Laboratory monitoring is not required for apixaban. Dosage adjustments are necessary in some patients. Apixaban may present an alternative option to currently available anticoagulants for the management and prevention of VTE.

REFERENCES

1. FDA approves Pradaxa to prevent stroke in people with atrial fibrillation. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm230241. Updated October 21, 2010. Accessed February 10, 2013.
2. FDA approves Xarelto to prevent stroke in people with common type of abnormal heart rhythm. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm278646.htm. Updated November 7, 2011. Accessed February 10, 2013.
3. Scaglione F. New oral anticoagulants: Comparative pharmacology with vitamin K antagonists. *Clin Pharmacokinet* 2013;52(2):69–82.
4. Wong PC, Pinto DJ, Zhang D. Preclinical discovery of apixaban, a direct and orally bioavailable factor Xa inhibitor. *J Thromb Thrombol* 2011;31(4):478–492.
5. Eliquis (apixaban), prescribing information. Princeton, N.J.: Bristol-Myers Squibb; 2012.
6. Prom R, Spinler SA. The role of apixaban for venous and arterial thromboembolic disease. *Ann Pharmacother* 2011;45(10):1262–1283.
7. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: Single-dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. *Br J Clin Pharmacol* 2013;75(2):476–487.
8. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor Xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation: The ARISTOTLE-J study. *Circ J* 2011;75(8):1852–1859.
9. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after

oral administration to humans. *Drug Metab Dispos* 2009;37(1):74–81.

10. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin Pharmacokinet* 2009;48(1):1–22.

11. Wang L, Zhang D, Raghavan N, et al. *In vitro* assessment of metabolic drug–drug interaction potential of apixaban through cytochrome P450 phenotyping, inhibition, and induction studies. *Drug Metab Dispos* 2010;38(3):448–458.

12. Wang L, Raghavan N, He K, et al. Sulfation of *O*-demethyl apixaban: Enzyme identification and species comparison. *Drug Metab Dispos* 2009;37(4):802–808.

13. Zhang D, He K, Raghavan N, et al. Comparative metabolism of 14C-labeled apixaban in mice, rats, rabbits, dogs, and humans. *Drug Metab Dispos* 2009;37(8):1738–1748.

14. Alexander JH, Becker RC, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: Results of the apixaban for prevention of acute ischemic and safety events (APPRAISE) trial. *Circulation* 2009;119(22):2877–2885.

15. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;365(8):699–708.

16. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364(9): 806–817.

17. Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: A predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol* 2012;11(3):225–231.

18. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981–992.

19. Easton JD, Lopes RD, Bahit MC, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: A subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012; 11(6):503–511.

20. Lassen MR, Davidson BL, Gallus A, et al. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost* 2007;5(12):2368–2375.

21. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011;365(23):2167–2177.

22. Lassen MR, Raskob GE, Gallus A, et al. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009;361(6):594–604.

23. Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): A randomised double-blind trial. *Lancet* 2010;375(9717):807–815.

24. Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363(26):2487–2498.

25. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*, December 8, 2012 (online).

26. Eliquis (apixaban). *Red Book Online*. Ann Arbor, Mich.: Truven Health; 2013. Available at: www.truvenhealth.com. Accessed February 10, 2013.

27. Xarelto (rivaroxaban). *Red Book Online*. Ann Arbor, Mich.: Truven Health; 2013. Available at: www.truvenhealth.com. Accessed February 10, 2013.

28. Pradaxa (dabigatran). *Red Book Online*. Ann Arbor, Mich.: Truven Health; 2013. Available at: www.truvenhealth.com. Accessed February 10, 2013.

29. Warfarin sodium. *Red Book Online*. Ann Arbor, Mich.: Truven Health; 2013. Available at: www.truvenhealth.com. Accessed February 10, 2013.

30. Lee S, Mullin R, Blazawski J, Coleman C. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. *PLoS One* 2012;7(10):e47473.

31. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: Systematic review, meta-analysis, and indirect treatment comparisons. *BMJ* 2012;344:e3675 (online). ■